Scientific Evidence for Medical Marijuana Use

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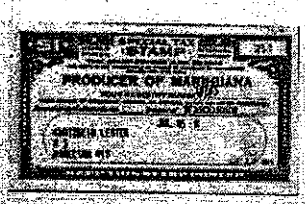
Marijuana, cannabis, hashish…These substances, commonly associated with negative connotations, are being considered for medicinal purposes. The topic has generated much public interest to assess the current knowledge on the therapeutic potential of cannabinoids. The history of medical marijuana use, its pharmacologic potential, and its untoward effects and common uses are reviewed.

History

Originating from Central Asia, cannabis is one of the oldest psychotropic drugs known to humanity. According to archeological discoveries, cannabis has been known in China at least since the Neolithic period, around 4000 BC.[1] In 2737 BC the Emperor of China, Shen Nung, described the properties and therapeutic uses of cannabis in his compendium.[2] Soon thereafter, the plant was cultivated for its fiber, seeds, recreational consumption and use in medicine. From China, cannabis spread to India, where in 1839 William O'Shaughnessy, a British physician and surgeon working in India discovered the analgesic, appetite stimulant, antiemetic, muscle relaxant and anticonvulsant properties of cannabis. The medical use of cannabis expanded quickly from there.[3] It was in 1854 that cannabis was listed in the United States Dispensatory and sold freely in pharmacies of Western countries.[4] However, over the next several decades the use of cannabis became responsible for insanity, moral and intellectual deterioration, violence and various crimes. The American authorities condemned its use after the prohibition of alcohol was lifted. Thus, in 1937, under pressure from the Federal Bureau of Narcotics and against the advice of the American Medical Association, the U.S. Government introduced the *Marihuana Tax Act:* a tax of $1 per ounce was collected when marijuana was used for medical purposes and $100 per ounce when it was used for unapproved purposes.[5] Cannabis was removed from the United States Pharmacopoeia in 1942, thus losing its therapeutic legitimacy. Despite its illegality, patients have continued to obtain cannabis on the black market for self-medication.



Chemistry

Cannabis is a leafy annual, with some species attaining heights of more than 10 feet. Each leaf has 5 to 10 leaflets radiating from the top of the stalk. These leaflets are soft textured, roughly 7 – 10 inches long, with regular dentations like a saw blade. The glandular hairs on the leaflets produce a resin mixture.[6] The two main preparations derived from cannabis are marijuana and hashish. Marijuana is a Mexican term initially attributed to cheap tobacco but referring today to dried leaves and flowers of the hemp plant. Hashish, the Arabic name for Indian hemp, is the viscous resin of the plant. There are several species of cannabis, with the most relevant being *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis.*[7] Cannabis contains more than 460 known isolated chemicals, greater than 60 of which are grouped under the name cannabinoids. Delta-9-tetrahydrocannabinol, a cannabinoid known as THC, is the major psychoactive ingredient of cannabis. Other cannabinoids present include delta-8-tetrahydrocannabinol, cannabinol, and cannabidiol (CBD), but they are present in small quantities and have no significant psychotropic effects compared to THC.[1] In addition to these compounds, marijuana contains alkaloids, steroidal compounds and mixtures of volatile components.[6]

Uses and Pharmacology

Marijuana exerts its action in the body following inhalation of the smoke or oral ingestion.[6] Once inhaled, THC is rapidly absorbed and distributed throughout the tissues of the body, particularly to tissues with high lipid content. It then exerts its action by binding to specific CB_1 and CB_2 cannabinoid receptors.

Toxicology

Marijuana has a strong potential for abuse and is classified as a schedule I drug.[6] It can be harmful to the heart, lungs, brain, endocrine system, and eyes.

After ingestion of marijuana, users may experience tachycardia, an increased heart rate, and an increase in blood pressure. Marijuana impairs reaction time, motor coordination, and visual perception. It can also produce panic attacks, "flashbacks", and other emotional disturbances. Reduced sperm counts, sperm structural abnormalities, and motility changes have all been reported in males. Abnormal menstruation has been associated with long-term marijuana use in females. Marijuana ingestion may also cause dry mouth, nausea, and vomiting.

Current Uses

Hype began to rise again in 1978 for the medicinal use of marijuana when Robert Randal, a glaucoma patient, began treating himself by smoking marijuana.[8] In response to a lawsuit filed by the patient the U.S. Government created a compassionate program for medical marijuana. Under this program, the U.S. Government supplied marijuana to a limited number of patients with debilitating diseases. In 1991, President Bush closed the program to new candidates due to a surge in new applications from AIDS patients. Seven of the original 20 patients continue to receive their marijuana.

Currently, marijuana is being investigated as an antiemetic[9-38] (Table 1.1-1.3), appetite stimulant[39-43] (Table 2.1-2.3), and as an analgesic[44-64] (Table 3.1-3.2). Studies have also been done looking at the use of marijuana in multiple sclerosis[37;65-77] (Table 4.1-4.5), epilepsy[78] (Table 5.1), glaucoma[79-81] (Table 6.1-6.4), Parkinson's disease[82;83] (Table 7.1-7.2) and Tourette's Syndrome (Table 8.1) Numerous case reports exist of patients testifying on the effectiveness of marijuana in their condition.

The evidence generated to date is summarized for the various uses of cannabis in the tables and is further subdivided by the route of administration and/or form of cannabis administered. For example, Nabilone, a synthetic cannabinoid, is used as an oral antiemetic in the treatment of refractory chemotherapy-induced nausea and vomiting in patients that have failed to respond to traditional antiemetic therapy.[84] There are 15 studies summarized in Table 1.3 where during the 1970's and 1980's nabilone was administered orally as an antiemetic to 600 patients suffering from various types of cancers.[7] It was the results of these randomized controlled studies demonstrating nabilone to be significantly superior to some of the conventional therapies that led to the approval of the drug in 1985. Nabilone is now marketed under the brand name Cesamet®, a schedule II controlled substance, with the usual recommended adult dosage 1 or 2 mg twice daily.[84] Researchers, in this case, identified the specific component of cannabis that is effective in suppressing emesis. This format to summarize the evidence is used in each of the 8 proposed uses

Conclusion

Cannabis is one of the oldest psychotropic drugs known to humanity. Its use has risen and fallen throughout the years, dating back to 4000 BC. Currently, research is being performed looking at the medicinal performance of marijuana in a number of diseases. The therapeutic potentials for cannabinoids include treatment of pain, lack of appetite, nausea, glaucoma, asthma, epilepsy, spasticity, and now tremors.[65] Tetrahydrocannabinol, the major active ingredient of marijuana, has prominent psychoactive properties that make it too toxic to justify its use where there are more specific therapies. Once a potential action of marijuana has been identified natural and synthetic analogs can be researched and tested to target the useful drug characteristic and reduce the nonspecific, often undesirable, actions. It is important to carefully sift through scientific studies to determine the superiority or inferiority of marijuana in comparison to placebo or active treatments before recommendations are made to alter the regulatory control related to marijuana possession and use.

Table 1. Antiemetic Effect in Cancer Chemotherapy

Table 1.1 Randomized Controlled Trials: Smoked Marijuana Cigarettes

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Levitt et al. (1984)[27] Canada	Adults with various tumors (ages 28-78)	20-Placebo Controlled Crossover Design	One marijuana cigarette + placebo oral THC x 4 times. Oral THC: 15 mg + placebo marijuana cigarette x 4 times	The treatments were effective only in 25% of the patients. 35% of the subjects preferred smoked marijuana and 45% had no preference	Seven persons exhibited distortions of time perception or hallucinations. Four with THC alone, two with marijuana alone, and one with both	Treatment effective in only 25% of patients, but 35% have important adverse events.
Chang et al. (1981)[12] United States	Patients with various tumors (ages 17-58)	8-Placebo Controlled Crossover Design	Oral THC 10 mg/m^2 x 5 times or smoked one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	No antiemetic effect of THC in this group of patients receiving cyclophosphamide or doxorubicin. Delta-9-tetrahydrocannabinol, in comparison with a placebo, did not significantly reduce the number of vomiting and retching episodes, volume of emesis, degree of nausea, or duration of nausea in comparison to placebo.	Euphoria (75%) and short lasting episodes of tachycardia	When vomiting was severe, the oral THC was replaced with the cigarette. No better than placebo, but significant undesired effects.
Chang et al. (1979)[11] United States	Patients with osteogenic sarcoma	15-Placebo Controlled Crossover Design	Oral THC 10 mg/m^2 x 5 times or smoked one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	Oral THC alone or the combination of oral and smoked THC had an antiemetic effect significantly superior to placebo. Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo. Delta-9-tetrahydrocannabinol was significantly more effective than placebo in reducing the number of vomiting and retching episodes ($p<0.02$), degree of nausea ($p<0.01$), duration of nausea ($p<0.01$), and volume of emesis ($p<0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured less than 5.0 ng/mL, 5.0 to 10.0 ng/mL, and greater than 10.0 ng/mL, the incidences of nausea and vomiting were 44%, 21%, and 6%, respectively.	Sedation in 80% of the patients	14 of 15 patients had a response greater than placebo. 80% did experience sedation.

Table 1.2 Randomized Controlled Trials: Oral THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
McCabe et al. (1988)[28] United States	Adults with various tumors (ages 18-69)	36-Crossover Design	Oral THC: 15mg/m^2 x 7 times. Oral prochlorperazine: 10mg x 7 times	Antiemetic effect of THC significantly superior to prochlorperazine. THC decreased nausea and vomiting in 23 of 36 patients (64%) compared to 1 of 36 receiving prochlorperazine	Frequent by transient dysphoria with THC	Superior to prochlorperazine, but frequent dysphoria
Levitt et al. (1984)[27] Canada	Adults with various tumors (ages 28-78)	20-Placebo Controlled Crossover Design	One marijuana cigarette + placebo oral THC x 4 times. Oral THC: 15 mg + placebo marijuana cigarette x 4 times	The treatments were effective only in 25% of the patients. 35% of the subjects preferred smoked marijuana and 45% had no preference	Seven persons exhibited distortions of time perception or hallucinations. Four with THC alone, two with marijuana alone, and one with both	Treatment effective in only 25% of patients, but 35% have important adverse events.
Gralla et al. (1984)[19] United States	Adults with various tumors (ages 39-72)	30-Parallel Group Design	Oral THC 10 mg/m^2 x 5 times: 15 patients. Metoclopramide IV: 10 mg/m^2 x 5 times: 15	Antiemetic effect of metoclopramide significantly superior to THC. Patients receiving metoclopramide had significantly fewer episodes of vomiting (median: two vs. eight) than those receiving THC ($p = 0.02$). Additionally, more of the patients who received	The two products induced frequent but generally well tolerated side effects. Main adverse reactions: THC: sedation (86%), dry mouth (80%),	Metoclopramide superior to THC, adverse events similar.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
			patients	metoclopramide (73% vs. 27%, $P = 0.01$) had major antiemetic control (defined as two or fewer vomiting episodes). The volume of emesis and the durations of nausea and vomiting were less for patients receiving metoclopramide; however, these differences were not significant ($P < 0.05$) in the small number of patients entered in this study.	dizziness (80%), orthostatic hypotension (53%), And euphoria (20%). Metoclopramide: sedation (93%), dry mouth (33%), dizziness (7%), euphoria (7%)	
Ungerleider et al. (1982)[85] United States	Adults with various tumors (ages 18-82)	172-Crossover Design	Oral THC: 7.5-12.5 mg x 4 times. Oral prochlorperazine 10 mg x 4 times	Antiemetic effect equivalent with THC and prochlorperazine. The level of nausea/vomiting experienced for patients on both protocol drugs on the single-day chemotherapy regimen was similar and there was no significant drug effect (analysis of variance: F = 0.00, NS). Nausea levels were initially higher in the multiple-day chemotherapy regimen sample and then dropped sharply over the first 12 hours. Overall, the average nausea score was lower than for patients on the single-day sample. In spite of this difference in time course there was still no significant difference between THC and prochlorperazine in antiemetic response (F = 0.12, NS). There were significant drug effects with THC less ability to concentrate ($p< 0.01$), less social interaction ($p< 0.05$), and less activity ($p< 0.05$)	Drowsiness, dizziness, concentration disorders, spatial-time distortions, euphoria, loss of activity and reduction of social interactions more frequent with THC than with prochlorperazine	Equally efficacious for emesis, but THC has significant decreases in concentration, social interaction and activity.
Neidhart et al. (1981)[29] United States	Patients with various tumors (median age: 45 years)	36-Crossover Design	Oral THC: 10 mg x (4-8) times. Oral haloperidol: 2 mg x (4-8) times	THC and haloperidol were equally effective in controlling nausea and vomiting as judged by number of vomiting episodes, patient evaluation of efficacy, and patient preference. Each group had roughly the same percentage of patients reach effective prevention of nausea and vomiting (41% for THC and 37% for haloperidol), effective relief of nausea and vomiting (51% THC and 49% haloperidol), fewer than five episodes of vomiting (26% THC and 35% haloperidol), and the mean number of vomiting episodes (9.9 THC and 13.2 haloperidol)	THC: toxicity in 94% of patients. The most frequent manifestations were drowsiness (58%), feeling faint (55%), euphoria (40%), spasms or tremors (15%). Toxicity interfered with function in 25% of the cases. Haloperidol : toxicity in 79% of the patients. The most frequent manifestations were drowsiness (36%), euphoria (30%), and spasms or tremors (18%). Toxicity interfered with function in 6% of the cases.	THC and haloperidol were equally effective in this small trial. The oral THC was less well tolerated than the haloperidol, but most patients had no serious side effects.
Chang et al. (1981)[17] United States	Patients with various tumors (ages 17-58)	8-Placebo Controlled Crossover Design	Oral THC 10 mg/m^2 x 5 times or smoked one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for subsequent doses)	No antiemetic effect of THC in this group of patients receiving cyclophosphamide or doxorubicin. Delta-9-tetrahydrocannabinol, in comparison with a placebo, did not significantly reduce the number of vomiting and retching episodes, volume of emesis, degree of nausea, or duration of nausea in comparison to placebo.	Euphoria (75%) and short lasting episodes of tachycardia	When vomiting was severe, the oral THC was replaced with the cigarette. No better than placebo, but significant undesired effects.
Colls et al. (1980)[13] New Zealand	Adults with solid tumors	35-Placebo-Controlled Crossover Design	Oral THC: 12mg/ m^2 x 3 times. Oral thiethylperazine: 6.6 mg/m^2 x 3 times. Metoclopramide IV: 4.5 mg/m^2 x 1 time	There were no significant differences in the antiemetic effects of these drugs.	Adverse effects, primarily of a neuropsychiatric nature, more frequent and severe with THC than with thiethylperazine or metoclopramide	Authors state that toral THC taken by mouth is not recommended as a routine antiemetic agent in cancer chemotherapy.
Sallan et al. (1980)[35] United States	Patients with various tumors (ages 9-70)	73-Crossover Design	Oral THC: 15 mg or 10 mg/m^2 x 3 times. Oral prochlorperazine 10 mg x 3 times	Antiemetic effect of THC significantly superior to prochlorperazine. Of 25 patients who were treated with both drugs and who expressed a preference, 20 preferred THC ($p=0.005$). Among patients under 20 years of age there was a higher proportion of complete responses to THC courses (15 of 20) than among older patients (21 of 59 courses; $p=0.004$).	Euphoria with THC frequent but well tolerated	Patients who received both drugs preferred the THC over prochlorperazine.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
				Increased food intake occurred more frequently with THC ($p=0.008$) and was associated with the presence of a "high."		
Orr et al. (1980)[32] United States	Adults with various tumors (ages 22-71)	55-Placebo Controlled Crossover Design	Oral THC: 7mg/m^2 x 4 times. Oral prochlorperazine: 7mg/m^2 x 4 times	Antiemetic effect of THC significantly superior to prochlorperazine. The antiemetic effect of prochlorperazine was not statistically better than that of placebo. Nausea was absent in 40 of 55 patients receiving THC, eight of 55 patients receiving prochlorperazine, and five of 55 in the placebo group. The antiemetic effect of THC appeared to be more efficacious for cyclophosphamide, fluorouracil, and doxorubicin hydrochloride, and less so for mechlorethamine hydrochloride and the nitrosureas. Tetrahydrocannabinol appears to offer significant control of nausea in most patients and exceeding by far that provided by prochlorperazine	THC: euphoria (82%), sedation (28%), transient loss of emotional or physical control (21%). Prochlorperazine: sedation (26%), dizziness (22%), dry mouth	Tetrahydrocannabinol appears to offer significant control of nausea in most patients and exceeding by far that provided by prochlorperazine however the incidence of adverse effects is higher.
Kluin-Nelemans et al. (1979)[24] Netherlands	Adults with Hodgkin or non-Hodgkin lymphoma (ages 21-53)	11-Placebo Controlled Crossover Design	Oral THC: 10mg/m^2 x 3 times	Antiemetic effect of THC significantly superior to placebo. Although THC had remarkable antiemetic effects, the side effects were severe	Dizziness (82%), hallucinations (45%), euphoria (36%), drowsiness (36%), derealization (18%), concentration disorders (18%). Some severe effects of THC resulted in stoppage of the clinical trial	Although THC had remarkable antiemetic effects, the side effects were severe. Most patients preferred the nausea and the vomiting to the use of THC.
Frytak et al. (1979)[17] United States	Adults with gastrointestinal tumors (median age: 61)	116-Placebo Controlled Parallel Group Design	Oral THC: 15 mg x 3 times: 38 patients. Oral prochlorperazine: 10 mg x 3 times: 41 patients. Placebo: 37 patients	Antiemetic effect equivalent with THC and prochlorperazine and superior to placebo. On day one, a higher percentage of placebo patients experienced some nausea or vomiting ($p<0.05$). The percentage of patients experiencing no nausea and vomiting on days 2-4 was higher in the prochlorperazine group, but was not significant ($p=0.22$)	More frequent and more severe with THC than with prochlorperazine. 12 patients receiving THC and 1 patient receiving prochlorperazine dropped out of the study due to intolerable central nervous system toxicity	The THC had superior antiemetic activity in comparison to placebo, but it showed no advantage over prochlorperazine. Central nervous system side-effects, however, were significantly more frequent and more severe with THC.
Chang et al. (1979)[11] United States	Patients with osteogenic sarcoma	15-Placebo Controlled Crossover Design	Oral THC 10 mg/m^2 x 5 times or smoked one marijuana cigarette containing 1.93% THC (in the case of a vomiting episode, oral THC is replaced by a marijuana cigarette for the subsequent doses)	Oral THC alone or the combination of oral and smoked THC had an antiemetic effect significantly superior to placebo. Fourteen of 15 patients had a reduction in nausea and vomiting on THC as compared to placebo. Delta-9-tetrahydrocannabinol was significantly more effective than placebo in reducing the number of vomiting and retching episodes ($p<0.02$), degree of nausea ($p<0.01$), duration of nausea ($p<0.01$), and volume of emesis ($p<0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured less than 5.0 ng/mL, 5.0 to 10.0 ng/mL, and greater than 10.0 ng/mL, the incidences of nausea and vomiting were 44%, 21%, and 6%, respectively.	Sedation in 80% of the patients	14 of 15 patients had a response greater than placebo. 80% did experience sedation.
Sallan et al. (1975)[34] United States	Adults with various tumors (ages 18-76)	20-Placebo Controlled Crossover Design	Oral THC: 15 mg or 10mg/m^2 x 3 times	Antiemetic effect of THC significantly superior to placebo. For all patients an antiemetic effect was observed in 14 of 20 tetrahydrocannabinol courses and in none of 22 placebo courses. For patients completing the study, response occurred in 12 of 15 courses of tetrahydrocannabinol and in none of 14 courses of placebo ($p< 0.001$).	Drowsiness in 2/3 of the patients. Euphoria in 13 patients	Oral THC has antiemetic properties significantly better than placebo in reducing vomiting but adverse events were common

Table 1.3 Randomized Controlled Trials: Synthetic Analogs

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Chan et al. (1987)[10] Canada	Patients with various tumors (ages: 3.5-17.8)	30-Crossover Design	Oral nabilone: 1-4 mg. Oral prochlorperazine: 5-20 mg	Antiemetic effect of nabilone significantly superior to prochlorperazine. The overall rate of improvement of retching and emesis was 70% during the nabilone and 30% during the prochlorperazine treatment cycles (p=0.003). 66% of the patients preferred nabilone, 17% preferred prochlorperazine and 17% expressed no preference (p=0.015). Lower doses of nabilone had equivalent efficacy and did not induce major side effects.	More frequent with nabilone than with prochlorperazine but generally well tolerated. Main side effects: nabilone: drowsiness (67%), dizziness (50%), mood disorders (14%). Prochlorperazine: drowsiness (17%), mood disorders(11%).	Nabilone appears to be safe and effective for children receiving cancer chemotherapy. Although major side effects may occur at higher dosages, nabilone is preferable to prochlorperazine because of improved efficacy
Crawford and Buckman (1986)[14] Great Britain	Ovarian cancer or germ cell tumors	32-Crossover Design	Oral nabilone: 1 mg x 5 times. Metoclopramide IV: 1mg/kg x 5 times	The occurrence and quantity of each emesis episode was recorded by nursing staff and a questionnaire was completed by patients regarding nausea and vomiting side effects ranking 0 (not nauseous at all) to 10 (very nauseous all the time). Antiemetic effect equivalent but insufficient with nabilone and metoclopramide. There was no significant difference shown between nabilone and metoclopramide on number of vomiting episodes (p>0.05), mean vomiting volume (p.0.1), and nausea (p.0.05), although a subgroup of patients enjoyed a substantial reduction in episodes of vomiting whilst receiving metoclopramide.	Main side effect of nabilone: drowsiness. Main side effect of metoclopramide: diarrhea. Only 7 patients received the planned 4 drug regimens, with the reason for withdrawal almost always being disease progression.	The anti-emetic effect was equivalent between the two drugs, but both were inadequate.
Niederle et al. (1986)[30] Germany	Adults with testicular cancer (ages 19-45)	20-Crossover Design	Oral nabilone: 2 mg x 2 times. Oral alizapride 150 mg x 3 times	Antiemetic effect of nabilone significantly superior to alizapride. 50% of the patients preferred nabilone, 35% preferred alizapride and 15% expressed no preference. Patients on nabilone had significantly fewer episodes of emesis than those on alizapride (medians, 1.1 vs. 2.9; p<0.01). Nabilone was superior to alizapride in giving complete relief from nausea (medians, 65% vs. 30%; p<0.01), and was more effective in shortening the duration of nausea (medians, 1.3 h vs. 5.1 h; p<0.01)	More frequent with nabilone than with alizapride. Main side effects: nabilone: drowsiness (80%), hypotension or tachycardia (70%), dry mouth (65%), apathy (15%), euphoria (10%), decreased concentration (10%). Alizapride: drowsiness (20%), extrapyramidal effects (20%), headaches (10%)	Nabilone has greater antiemetic activity than alizapride in young patients. Nabilone dosage should be reduced to decrease the incidence and degree of adverse reactions.
Pomeroy et al. (1986)[33] Ireland	Adults with various tumors (ages 21-66)	38-Parallel Group Design	Oral nabilone: 1 mg x 3 times: 19 patients. Oral domperidone: 20 mg x 3 times: 19 patients	Antiemetic effect of nabilone significantly superior to domperidone. The mean number of vomiting episodes in cycle 1 was 4.76 for nabilone and 12.95 for domperidone (p< 0.02). The corresponding values for cycle 2 were 4.27 and 7.69 (p>0.10), and for cycles 1 and 2 combined, 4.53 for nabilone and 10.81 for domperidone (p<0.01). Nausea and food intake scores did not differ significantly, although there was a trend towards less nausea and an increased food intake with nabilone	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (58%), dizziness (58%), dry mouth (53%), postural hypotension (21%), euphoria (11%), headaches (11%), And lightheadedness (11%). Domperidone: drowsiness (47%), dry mouth (42%), dizziness (21%), headaches (16%)	Nabilone is superior to domperidone for the control of cytotoxic-induced emesis. Subjectively adverse effects were more frequent with nabilone and included drowsiness, dizziness, dry mouth, and postural hypotension.
Dalzell et al. (1986)[15] Great Britain	Patients with various tumors (ages 10 months-17 years)	18-Crossover Design	Oral nabilone: 1-3 mg. Oral domperidone: 15-45 mg	Antiemetic effect of nabilone significantly superior to domperidone in both mean number of vomits (5.94 vs. 16.72, p<0.01) and mean severity of nausea (1.50 vs. 2.50, p=0.01). Most patients or their parents preferred nabilone for continuous use (12 vs. 1)	More frequent with nabilone than with domperidone but generally well tolerated. Main side effects: nabilone: drowsiness (55%), dizziness (36%), And mood changes (14%). Domperidone: drowsiness (27%), dizziness (5%), mood changes (5%)	Nabilone is an effective antiemetic for children on chemo-therapy. It seems to be superior to domperidone, and has a higher incidence of side effects.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Niiranen and Mattson (1985)[31] Finland	Adults with lunch cancer (ages 48-78)	24-Crossover Design	Oral nabilone: 1 mg x 2-4 times. Oral prochlorperazine 7.5 mg x 2-4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine. 2/3 of the patients preferred nabilone to prochlorperazine	More frequent with nabilone than with prochlorperazine. Three patients dropped out of the study due to decreased coordination and hallucinations induced by nabilone. Main side effects of nabilone: vertigo (48%), dry mouth (26%). Prochlorperazine only induced drowsiness in one patient	Nabilone was significantly superior to prochlorperazine in the reduction of vomiting episodes. Side effects, mainly vertigo, were evident in nearly half of the patients after nabilone.
Hutcheon et al. (1983)[21] Great Britain	Patient with various tumors (ages 17-80)	108-Single Blind Parallel Group Design	Levonantradol IM (synthetic cannabinoid): 0.5 mg x 4 times: 27 patients; 0.75 mg x 4 times: 28 patients; 1 mg x 4 times: 26 patients; chlorpromazine IM 25 mg x 4 times: 27 patients	The extent of anorexia, nausea, and vomiting were assessed at regular intervals. In addition, a self assessment questionnaire was completed by the patient. Antiemetic effect of levonantradol (0.5 mg) significantly superior to chlorpromazine (25 mg). High doses of levonantradol did not increase its efficacy and were accompanied by a greater toxicity.	Levonantradol (0.5) and chlorpromazine (25 mg) were reasonably well tolerated. They mainly cause drowsiness and dizziness with equivalent frequency. 0.75 mg and 1 mg doses of levonantradol induce significant, sometimes unacceptable toxicity	Neither drug achieved satisfactory control of vomiting. But authors concluded that levonantradol (0.5 mg) is a more effective than chlorpromazine (25 mg) in patients receiving cytotoxics.
Ahmedzai et al. (1983)[9] Scotland	Patients with lung cancer (ages 27-72)	26-Crossover Design	Oral nabilone: 2 mg BID. Oral prochlorperazine 10 mg TID	Antiemetic effect of nabilone significantly superior to prochlorperazine. Symptom scores were significantly better for patients on nabilone for nausea, retching and vomiting ($p<0.05$). Fewer subjects vomited with nabilone ($p=0.05$) and the number of vomiting episodes was lower ($p<0.05$); no patients on nabilone required additional parenteral anti-emetic. More patients preferred nabilone for anti-emetic control ($p<0.005$). 62% of patients preferred nabilone for continuous use.	More frequent with nabilone than with prochlorperazine. Main side effects: nabilone: drowsiness (57%), postural dizziness (35%), euphoria (21%), drunk-feeling (18%), And lightheadedness (18%). Prochlorperazine: drowsiness (27%)	Side effects with nabilone were more frequent, but more patients preferred nabilone for anti-emetic control.
George et al. (1983)[18] France	>Women with advanced gynecological tumors (median age: 54 years)	20-Crossover Design	Oral nabilone 1 mg x 3 times. Chlorpromazine IM 12.5 mg x 1 time	Antiemetic effect equivalent but insufficient with nabilone and chlorpromazine at doses used. Nabilone, in comparison with chlorpromazine did not significantly reduce the number of vomiting. Ten patients preferred nabilone, 5 preferred chlorpromazine and 3 were undecided.	More frequent with nabilone than with chlorpromazine but their extent never required specific treatment. Main side effects: nabilone: dry mouth (80%), drowsiness (60%), and inebriated sensations (40%), postural hypotension (35%). Chlorpromazine: dry mouth (40%), drowsiness (27%)	Nabilone, in comparison with chlorpromazine did not significantly reduce the number of episodes of vomiting. Ten patients preferred nabilone, 5 preferred chlorpromazine and 3 were undecided.
Levitt (1982)[26] Canada	Patients with various tumors (ages 17-78)	36-Placebo Controlled Crossover Design	Oral nabilone: 2 mg x 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: vertigo (67%), drowsiness (61%), depersonalization (35%), dry mouth (24%), disorientation (16%). Five patients dropped out of the study due to side effects caused by nabilone	Nabilone significantly better than placebo, but greater side effects, causing 5 of 36 to withdraw.
Jones et al. (1982)[23] United States	Adults with various tumors	24-Placebo Controlled Crossover Design	Oral nabilone 2 mg x 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (65%), drowsiness (51%), dry mouth (31%), sleep disorders (14%). 11 patients dropped out of the study due to side effects caused by nabilone	Nabilone significantly better than placebo, but greater side effects, causing 11 of 24 to withdraw.
Wada et al. (1982)[38] United States	Adults with various tumors (ages 18-81)	84-Placebo Controlled Crossover Design	Oral nabilone 2 mg x 2 times	Antiemetic effect of nabilone significantly superior to placebo	Frequent: dizziness (40%), drowsiness (34%), dry mouth (28%), euphoria (25%), dysphoria (10%). Generally mild or moderate except in 11 patients who reported severe reactions which led 8 of them to terminated the study	Nabilone significantly better than placebo, but greater side effects, causing 8 of 84 to withdraw.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Johansson et al. (1982)[22] Finland	Adults with various tumors (ages 18-70)	18-Crossover Design	Oral nabilone: 2 mg BID. Oral prochlorperazine 10 mg BID	Antiemetic effect of nabilone significantly superior to prochlorperazine. 72% of patients preferred nabilone for continuous use.	More frequent and more severe with nabilone than with prochlorperazine. Main side effects: nabilone: postural hypotension (42%), dizziness (23%), And mood disorders (8%). Prochlorperazine: headaches (13%), postural hypotension (9%), dizziness (9%)	Nabilone significantly superior to prochlorperazine, but has greater side effects. Nonethe less, patients preferred nabilone.
Einhorn et al. (1981)[16] United States	Patients with various tumors (ages 15-74)	80-Crossover Design	Oral nabilone: 2mg x 4 times. Oral prochlorperazine 10 mg x 4 times	Antiemetic effect of nabilone significantly superior to proclilorperazine. 75% of patients preferred nabilone for continuous use. Patients experienced nausea on both arms of the crossover, but nausea was not as severe or prolonged on nabilone ($p< 0.001$). Frequency of vomiting was significantly less in the nabilone group compared to prochlorperazine on all 5 days. Day one frequency of vomiting was 7.05 with nabilone compared to 10.30 with prochlorperazine ($p<0.001$). Day two, 2.05 vs. 5.09 ($p<0.001$). Day three, 1.08 vs. 3.80 ($p<0.001$). Day 4, 1.24 vs. 3.24 ($p<0.001$). Day 5, 1.12 vs. 2.97 ($p<0.001$)	Hypotension, euphoria, drowsiness, and lethargy more pronounced with nabilone	Antiemetic effect of nabilone superior to prochlorperazine. 75% of patients preferred nabilone for continuous use. Side effects consisting of hypotension and lethargy were more pronounced with nabilone.
Steele et al. (1980)[16] United States	Adults with various tumors (ages 19-65)	37-Crossover Design	Oral nabilone: 2 mg x 2 times. Oral prochlorperazine 10 mg x 2 times	Antiemetic effect of nabilone superior to prochloperazine. Patients received one of the following as the primary emetic stimulus: high-dose cis-dichlorodiammineplatinum(II) (DDP), low-dose DDP, mechlorethamine, streptozotocin, actinomycin D, or DTIC. Although results varied according to strength of emetic stimulus received, both nabilone and prochlorperazine appeared to produce antiemetic effects. Eighteen of the 37 patients achieved a complete or partial elimination of symptoms: seven with nabilone alone, three with prochlorperazine alone, and eight with each drug. Nabilone appeared to be the more effective antiemetic for patients who received chemotherapy agents other than high dose DDP; it was equivalent to prochlorperazine for those who did receive high-dose DDP.	Nabilone: drowsiness (47%), dizziness (36%), dry mouth (25%), euphoria (19%), postural hypotension (17%). These side effects were severe enough to prohibit or modify the use of nabilone in 25% of patients. Prochlorperazine: drowsiness (35%), dizziness (9%), dry mouth (5%). These side effects were mild	Nabilone appeared to be the more effective antiemetic for patients who received chemotherapy agents other than high dose DDP; it was equivalent to prochlorperazine for those who did receive high-dose DDP. Side effects from nabilone were dose-limiting in 25% of patients
Herman et al. (1979)[20] United States	Patients with various tumors (ages 15-74)	113-Crossover Design	Oral nabilone: 2 mg x 3 or 4 times. Oral prochlorperazine 10 mg x 3 or 4 times	Antiemetic effect of nabilone significantly superior to prochlorperazine. The patients clearly favored nabilone for continuous use. Of 113 patients evaluated, 90 (80%) responded to nabilone therapy, whereas only 36 (32%) responded to prochlorperazine ($p<0.001$). Complete relief of symptoms was infrequent, occurring only in nine patients (8%) given nabilone. When both drugs were compared, both nausea ($p< 0.01$) and vomiting episodes ($p< 0.001$) were significantly lower in patients given nabilone. Moreover, patients clearly favored nabilone for continued use ($p< 0.001$).	Drowsiness, dry mouth and dizziness observed with both products but twice as frequent and often more severe with nabilone. Four patients taking nabilone exhibited undesirable effects which required medical attention: hallucinations in three patients and hypotension in one patient. Euphoria associated with nabilone was infrequent (16% of cases) and mild	When both drugs were compared, both nausea and vomiting episodes were significantly lower in patients given nabilone. Patients clearly favored nabilone for continued use.

Table 2 Appetite Stimulation in Cancer or HIV/AIDS

Table 2.1 Randomized Controlled Trials: Smoked Marijuana Cigarettes

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Abrams et al. (2003)[39] United States	Adults with HIV infection	67-Placebo Controlled Parallel Group Design	Smoked THC: one to three marijuana cigarettes per day containing 3.95% THC; n=21 patients. Oral THC: 2.5 mg TID; n=25 patients. Placebo; n =21 patients	Weight gain equivalent with smoked THC and oral THC and statistically superior to placebo after 21 days of treatment. Oral THC group: average weight gain of 3.0 kg (p=0.021). Smoked THC group: average weight gain of 3.2 kg (p=0.004). Placebo group: average weight gain of 1.1 kg.	Generally well tolerated. One patient in the smoked THC group dropped out of the study due to grade 2 neuropsychiatric troubles. Two patients in the oral THC group dropped out of the study due to side effects, Grade 2 paranoia (1), persistent headache and nausea (1)	Effect is greater than placebo, but we do not know how it compares with other treatments.

Table 2.2 Randomized Controlled Trials: Oral THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Strasser et al. (2006)[42] Switzerland	Adults with advance cancer (>5% weight loss over 6 months)	164	*Cannabis sativa* extract: 2.5 mg THC + 1 mg CBD: 66 patients. Oral THC: 2.5 mg: 65 patients. Placebo: 33 patients	Appetite, mood, and nausea were monitored daily using the visual analog scale. Quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Increased appetite was reported by 75% in the THC + CBD, 60% for THC, and 72% receiving placebo, no significant difference was shown (p=0.068). There was no significant difference in quality of life in THC + CBD was compared with placebo (p=0.83), and when THC was compared to placebo (p=0.43).	Severe AEs were mainly dizziness, nausea/vomiting, and dyspnea	No different from placebo.
Abrams et al. (2003)[39] United States	Adults with HIV infection	67-Placebo Controlled Parallel Group Design	Smoked THC: one to three marijuana cigarettes per day containing 3.95% THC; n=21 patients. Oral THC: 2.5 mg TID; n=25 patients. Placebo; n =21 patients	Weight gain equivalent with smoked THC and oral THC and statistically superior to placebo after 21 days of treatment. Oral THC group: average weight gain of 3.0 kg (p=0.021). Smoked THC group: average weight gain of 3.2 kg (p=0.004). Placebo group: average weight gain of 1.1 kg.	Generally well tolerated. One patient in the smoked THC group dropped out o the study due to grade 2 neuropsychiatric troubles. Two patients in the oral THC group dropped out of the study due to side effects, Grade 2 paranoia (1), persistent headache and nausea (1)	Effect is greater than placebo, but we do not know how it compares with other treatments.
Jatoi et al. (2002)[41] United States	Adults with advanced cancers, weight loss of 2.3 kg or more over the past 2 months and/ or intake of less than 20 calories/kg/day	469-Parallel Group Design	Oral THC: 2.5 mg BID: 152 patients. Oral megestrol (synthetically derived progesterone): 800 mg: 159 patients. Oral THC: 2.5 mg BID + oral megestrol 800 mg: 158 patients	In monotherapy, megestrol stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC stimulated appetite in 49% of the patients and caused a weight gain in 3% of the patients. These two difference were statistically significant (p=0.0001 for appetite) (p=0.02 for weight gain). Combined therapy did not confer additional benefits compared with megestrol alone	Main side effects: THC: drowsiness (36%), confusion (24%), loss of coordination (15%). Megestrol: drowsiness (33%), confusion (21%), male impotence (18%), fluid retention (18%), loss of coordination (16%). THC + megestrol: drowsiness (39%), confusion (21%), loss of coordination (18%), male impotence (14%), fluid retention (13%)	Megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with THC alone. Combination therapy did not appear to confer additional benefit.
Beal et al. (1995)[40] United States	Patients with AIDS and weight loss of 2.3 kg or more	139-Placebo Controlled Parallel Group	Oral THC: 2.5 mg BID: 72 patients. Placebo: 67 patients	THC induced a marked, statistically significant stimulation of appetite. THC was associated with increased appetite above baseline (38% vs. 8% for placebo, P = 0.015), improvement in mood (10% vs. -2%, P = 0.06), and decreased nausea (20% vs. 7%; P = 0.05). Weight was stable in THC patients, while placebo	Generally minor or moderate. Main side effects: euphoria (12.5%), dizziness (7%), confusion (7%), drowsiness (6%)	Appetite increased, with minor adverse effects.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
		Design		recipients had a mean loss of 0.4 kg (P = 0.14). Of the dronabinol patients, 22% gained > or = 2 kg, compared with 10.5% of placebo recipients (P = 0.11).		
Struwe et al, (1993)[43] United States	Symptomatic HIV infection and weight loss of 2.3 kg or more	12 men-Placebo Controlled Crossover Design	Oral THC: 5 mg BID	THC stimulated appetite but the weight variation observed on THC and on placebo was statistically insignificant. Median weight gain of THC was 0.5 kg, a trend toward weight gain (p=0.13). Median weight loss on placebo was 0.7 kg	Seven patients withdrew (two because of drug intolerance, two because of disease progression, two because of noncompliance, and one because of experimental antiretroviral therapy)	In a selected group of HIV-infected patients with weight loss, short-term treatment with dronabinol may result in improvement in nutritional status and symptom distress.

Table 2.3 Randomized Controlled Trials: Oral THC + CBD

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Strasser et al. (2006)[42] Switzerland	Adults with advance cancer (>5% weight loss over 6 months)	164	*Cannabis sativa* extract: 2.5 mg THC + 1 mg CBD: 66 patients. Oral THC: 2.5 mg: 65 patients. Placebo: 33 patients	Appetite, mood, and nausea were monitored daily using the visual analog scale. Quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Increased appetite was reported by 75% in the THC + CBD, 60% for THC, and 72% receiving placebo, no significant difference was shown (p=0.068). There was no significant difference in quality of life when THC + CBD was compared with placebo (p=0.83), and when THC was compared to placebo (p=0.43).	Severe AEs were mainly dizziness, nausea/vomiting, and dyspnea	No different from placebo.

Table 3 Analgesia

Table 3.1 Randomized Controlled Trials: Smoked Marijuana Cigarettes

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Ellis et al. (2009)[48] United States	Neuropathic pain in HIV	28-Placebo Controlled Crossover Design	Smoked cannabis (.1-8% THC depending on tolerability, and pain control) or identical placebo cigarettes QID for 5 consecutive days	Primary outcome measured was change in pain intensity as measured by the Descriptor Differential Scale. Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size=0.60; p<0.016). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95%CI 0.28, 0.65) and 0.18 (0.03, 0.32).	Most were mild and self limiting, two subjects experienced treatment-limiting toxicities. One cannabis-naive subject had an acute, cannabis-induced psychosis at the start of the second smoking week. A second subject developed an intractable, smoking-related cough during cannabis treatment; symptoms resolved spontaneously after smoking cessation. A third subject experienced intractable diarrhea deemed unlikely to be related to study treatments. Some nontreatment-limiting side effects were greater for cannabis than placebo and were concentration difficulties, fatigue, sleepiness or sedation.	Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV-associated distal sensory predominant polyneuropathy .
Wilsey et al. (2008)[64] United States	Central and peripheral neuropathic pain	38-Placebo Controlled Crossover Design	High-dose cannabis (7% THC), low-dose cannabis (3.5% THC), and placebo cigarettes.	The primary outcome measured was spontaneous pain relief, using the visual analog scale. 0 (no pain), 100 (worst possible pain). The primary analysis compared patients' mean VAS pain intensity before and after smoking marijuana. A "ceiling effect" was noted with cumulative dosing as the 3.5% and 7% cigarettes produced equal antinociception at every time point with no difference between the 3.5% and7% doses over time (treatment by time interaction: p=0.95). Significant analgesia expressed as a 0.0035 reduction in VAS pain intensity per minute was noted from both 3.5% and 7% cannabis compared with placebo (combined 3.5% and 7% treatment group vs placebo difference per minute -0.0035, 95% CI: [– 0.0063,– 0.0007], p=0.016). Secondary outcomes, from the neuropathic pain scale Modeling of sharp (p<0.001), burning (p< 0.001), aching (P < .001), sensitive (p<0.03), superficial (p< 0.01) and deep pain (p<0.001) showed that cannabis improved pain scores more than placebo. Cannabis provided a greater degree of relief on the global impression scale (p<0.01).	No effect on evoked pain was seen. Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at higher doses.	Cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. However, the use of marijuana as medicine may be limited by its method of administration (smoking) and modest acute cognitive effects, particularly at higher doses.
Abrams et al. (2007)[44] United States	HIV-associated sensory neuropathy	50	Smoked cannabis (3.56% THC) or identical placebo cigarettes TID for 5 days	Over a 5 day period, smoking cannabis cigarettes TID significantly reduced HIV-SN pain compared to placebo	No serious adverse events reported.	Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV.
Wallace et al. (2007)[63] United States	Capsaicin-induced pain and hyperalgesia	15 Healthy Volunteers	Each subject received placebo and 3 doses of smoked cannabis (2%, 4%, or 8% THC) given in a random order	5 minutes after cannabis administration, no dose showed effect on capsaicin induced pain. 45 minutes after cannabis administration, there was a significant decrease in capsaicin induced pain seen with the medium (4% THC) and a significant increase in pain seen with the high dose (8%). There was no effect seen with the low dose at 45 minutes. No effect on the area of hyperalgesia at any dose.	Generally well tolerated. Dyspnea, dry mouth, feeling cold, and somnolence were all reported.	This study suggests that there is a window of modest analgesia for smoked cannabis, with lower doses decreasing pain and higher doses increasing pain.

Table 3.2 Randomized Controlled Trials: THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Notcutt et al. (2004)[55] Great Britain	Chronic Pain	34	THC: 2.5mg in sublingual spray for 4 weeks.; Cannabidiol (CBD) 2.5mg in sublingual spray for 4 weeks; THC: 2.5mg + CBD 2.5mg in sublingual spray for 4 weeks	Pain relief and improvement of sleep quality with THC alone and the THC-CBD combination. Mean percentage of good night sleep was THC + CBD 55.4%, THC 42.9%, CBD 36.9%, and placebo 17% ($p<0.001$) CBD alone ineffective.	Dry mouth, drowsiness, euphoria/dysphoria, dizziness	THC alone and combined with CBD provided pain relief, CBD alone was ineffective.
Berman et al. (2004)[45] Great Britain	Central neuropathic pain associated with brachial plexus root avulsion	48	THC: 2.7mg in sublingual spray or THC: 2.7mg + CHB 2.5mg in sublingual spray for three periods of 2 weeks	Statistically significant decrease ($p=0.005$) in pain and statistically significant improvement in sleep quality with THC alone and the THC-CBD combination	Three patients dropped out of the study, including two due to adverse effects of THC; side effects generally mild to moderate in other patients	Pain severity and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated.
Naef et al. (2003)[54] Switzerland	Experimental pain conditions (heat, cold, pressure, single and repeated transcutaneous electrical stimulation)	12 healthy cannabis-naïve volunteers	THC: 20 mg (capsules); morphine: 30 mg (capsules); THC: 20 mg + morphine 30 mg (capsules). The three regimens were administered as single oral doses.	THC did not significantly reduce pain in any test compared to placebo; in the cold and heat tests, THC even produced hyperalgesia which is completely neutralized by THC-morphine; THC-morphine had a slight additive analgesic effect in the electrical stimulation test; THC-morphine had no analgesic effect in the pressure test	Sleepiness (12), dry mouth (12), vertigo (11), altered perception (10), euphoria (9), confusion (7), and strange thought (7) are common but usually mild	THC did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia. Psychotropic and somatic side-effects were common, but usually mild .
Buggy et al. (2003)[47] Great Britain	Postoperative pain (hysterectomy)	40	Oral THC: 5 mg: 20 patients; placebo: 20 patients	No analgesic effect of THC on postoperative pain. No difference in summed pain intensity at 6 hours between the groups (placebo 7.9, THC 4.3), and time to rescue analgesia (placebo 217 minutes, THC 163 minutes.)	Increased awareness of surroundings	Study demonstrates no evidence of an analgesic effect of orally administered delta-9-THC 5 mg in postoperative pain.
Holdcroft et al. (1997)[49] Great Britain	Chronic pain - gastrointestinal (Mediterranean fever)	1 (N of 1 Trial)	Oral cannabis extract containing 10 mg of THC x 5 times/day for 3 weeks	Statistically significant reduction in morphine consumption with THC intake ($p<0.001$)	Nausea and vomiting	No anti-inflammatory effects of THC were detected in this single patient, but a reduction in additional analgesic requirements was achieved.
Raft et al. (1977)[59] United States	Dental extraction pain	10	THC IV: 0.22 and 0.44 mg/k; diazepam 0.157mg/kg	No analgesic effect of THC on postoperative pain	0.22 mg/kg dose of THC: euphoria/dysphoria; 0.44 mg/kg dose of THC: anxiety	THC injection had a poor analgesic response .
Noyes et al. (1975)[57] United States	Cancer pain	10	Oral THC: 5, 10, 15, and 20 mg (capsules)	Pain relief with the 15 and 20 mg doses. Pain Reduction 15mg: 3.6; 20 mg: 4.6; Placebo 0.9 ($p<0.025$)	Frequent drowsiness and confusion	Analgesia was obtained at the higher doses, but they also had higher side effects.
Noyes et al. (1975)[56] United States	Cancer pain	36	Oral THC: 10 and 20 mg (capsules) ; oral codeine: 60 and 120 mg	Pain relief equivalent with 10 mg of THC and 60 mg of codeine, as well as with 20 mg of THC and 120 mg of codeine	THC, 10 mg: well tolerated; THC, 20 mg: drowsiness, dizziness, ataxia, confusion and frequent mental disorders	THC 10 mg is about equivalent to codeine 60 mg. At a dose of 20 mg, however, THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
						Induced side effects that would prohibit its therapeutic use including somnolence, dizziness, ataxia, and blurred vision.

Table 3.3 Randomized Controlled Trials: Oral cannabidiol (CBD)

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Notcutt et al. (2004)[55] Great Britain	Chronic Pain	34	THC: 2.5mg in sublingual spray for 4 weeks.; Cannabidiol (CBD) 2.5mg in sublingual spray for 4 weeks; THC: 2.5mg + CBD 2.5mg in sublingual spray for 4 weeks	Pain relief and improvement of sleep quality with THC alone and the THC-CBD combination. Mean percentage of good night sleep was THC + CBD 55.4%, THC 42.9%, CBD 36.9%, and placebo 17% ($p<0.001$) CBD alone ineffective	Dry mouth, drowsiness, euphoria/dysphoria, dizziness	THC alone and combined with CBD provided pain relief, CBD alone was ineffective.
Lindstrom et al. (1987)[53] Sweden	Chronic neuropathic pain	10	Oral cannabidiol 450 mg/day in three split doses for 1 week.	No analgesic effect of cannabidiol	Sedation in seven patients	No analgesic effect, but significant sedation in 70% of the patients.

Table 3.4 Randomized Controlled Trials: THC + CBD sublingual spray

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Nurmikko et al. (2007) [58] United Kindom	Neuropathic pain characterized by allodynia	125	THC: 2.7 mg + CBD 2.5 mg self titrating regimen, 63 patients; Placebo, 62 patients for 5 weeks	The mean reduction in pain intensity score was greater in patients receiving THC + CBD vs. placebo, -1.48 vs. -0.52 respectively ($p=0.004$), improvements on neuropathic pain score ($p=0.007$), and patients global impression of change ($P<0.001$)	Sedative and gastrointestinal effects more commonly reported in those with active drug	Significant reduction in pain intensity score, but more common sedation and GI effects than placebo.
Rog et al. (2007)[61] United Kindom	Central pain in Multiple Sclerosis	63 entered this 2 year open label extension trial	All patients continued the 2 year follow up on THC: 2.7mg + CBD: 2.5mg per spray	Mean NRS-11 pain scores in the final week of the randomized trial were 3.8 in the treatment group vs. 5.0 in the placebo group. After the 2 year follow up, the mean NRS-11 pain score was 2.9.	Most common reported events were dizziness (27%), nausea (18%), and feeling intoxicated (11%).	THC/CBD was effective, with no evidence of tolerance. 92% of patients experienced an adverse event, most of which were mild.
Blake et al. (2006)[46] United Kindom	Pain associated with Rheumatoid Arthritis	58-Placebo Controlled Parallel Group Design	THC (2.7 mg) + CBD (2.5 mg)/spray. Max 6 sprays/evening: 31 patients. Placebo: 27 patients.	Statistically significant improvements in pain on movement ($p=0.044$), pain at rest ($p=0.018$), quality of sleep ($p=0.027$),DAS28 ($p=0.002$) and the SF-MPQ pain at present ($p=0.016$) component were seen following CBM + THC in comparison with placebo	Adverse effects were mild to moderate and there were no adverse effects related to withdrawal or serious adverse effects in the treatment group	A significant analgesic effect was observed and disease activity was significantly suppressed following THC-CBD treatment. The differences are small and variable across the population,

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
						they represent benefits of clinical relevance and show the need for more detailed investigation in this indication.
Rog et al. (2007)[60] United Kindom	Central pain in Multiple Sclerosis	64	THC: 2.7 mg + CBD: 2.5 mg per spray self titrating regimen. Max 48 sprays in 24 hours, 34 patients, Placebo, 30 patients	THC + CBD was superior to placebo in reducing the mean intensity of pain, -2.7 vs. -1.4 (p=0.005), and sleep disturbances - 2.5 vs. -1.7 (p=0.003)	More patients on THC + CBD report dizziness, dry mouth and somnolence.	Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated.
Notcutt et al. (2004)[53] Great Britain	Chronic Pain	34	THC: 2.5mg in sublingual spray for 4 weeks ; Cannabidiol (CBD) 2.5mg in sublingual spray for 4 weeks; THC: 2.5mg + CBD 2.5mg in sublingual spray for 4 weeks	Pain relief and improvement of sleep quality with THC alone and the THC-CBD combination. Mean percentage of good night sleep was THC + CBD 55.4%, THC 42.9%, CBD 36.9%, and placebo 17% (p<0.001) CBD alone ineffective	Dry mouth, drowsiness, euphoria/dysphoria, dizziness	THC alone and combined with CBD provided pain relief, CBD alone was ineffective.
Berman et al. (2004)[45] Great Britain	Central neuropathic pain associated with brachial plexus root avulsion	48	THC: 2.7mg in sublingual spray or THC: 2.7mg + CHB 2.5mg in sublingual spray for three periods of 2 weeks	Statistically significant decrease (p=0.005) in pain and statistically significant improvement in sleep quality with THC alone and the THC-CBD combination	Three patients dropped out of the study, including two due to adverse effects of THC; side effects generally mild to moderate in other patients	Pain severity and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated.

Table 3.5 Randomized Controlled Trials: Synthetic Analogs

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Skrabek et al. (2008)[86] Canada	Fibromyalgia	40	0.5mg nabilone/day titrated up to 1mg BID for 4 weeks or placebo	There were significant decreases in the Visual Analog Scale (-2.04, P < .02), Fibromyalgia Impact Questionnaire (-12.07, P < .02), and anxiety (-1.67, P < .02) in the nabilone treated group at 4 weeks.	The most common side effects reported by subjects in the nabilone group include drowsiness (7/15), dry mouth (5/15), vertigo (4/15), and ataxia (3/15). No serious adverse events occurred during the study.	Nabilone improved symptoms and was well-tolerated, so it may be a useful adjunct for pain management in fibromyalgia
Pinsger et al. (2006)[87] Austria	Chronic pain	30-Placebo Controlled Crossover Design	Oral nabilone (1/4 - 1mg/day) vs. placebo	Decrease of the average spinal pain intensity within the last 4 weeks (DeltaVAS) 0.9, decrease of the current spinal pain intensity (DeltaVAS) 0.6 (p = .006).		A majority of patients with chronic pain benefit from the addition of nabilone to the standard treatment.

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Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Wissel et al. (2006)[88] Austria	Chronic upper motor neuron syndrome (UMNS)	13-Placebo Controlled Crossover Design	Oral nabilone (1mg) vs. placebo	The 11-Point-Box-Test showed a significant decrease of pain under Nabilone ($p < 0.05$), while spasticity, motor function and activities of daily living did not change.	5 patients reported side effects: one moderate transient weakness of the lower limbs (Nabilone phase, drop out), three mild drowsiness (two Nabilone, one placebo) and one mild dysphagia (placebo).	Nabilone 1 mg per day proved to be a safe and easily applicable option in the care of patients with chronic UMNS and spasticity-related pain otherwise not controllable.
Karst et al. (2003)[52]	Chronic neuropathic pain	21	Oral CT-3 (10 mg capsules): 40 mg/day for the first 4 days followed by 80 mg/day for the next 3 days (synthetic analog of 11-hydroxy-THC)	CT-3 in both doses was more effective than placebo in relieving pain. Mean reduction in Visual Analog Pain scale at 3 hours were -11.54 in treatment group vs. 9.86 in placebo ($p=0.02$) Greater pain-reducing effects at 3 hours after intake than at 8 hours.	No major adverse effects	CT-3 was effective in reducing chronic neuropathic pain compared with placebo. No major adverse effects were observed.
Jain et al. (1981) United States	Postoperative or trauma pain	56	Levonantradol IM 1.5; 2; 2.5; and 3 mg (synthetic cannabinoid): 1.5 mg, 10 patients; 2 mg, 10 patients; 2.5 mg, 10 patients; 3 mg, 10 patients; placebo, 16 patients	Pain relief with the four doses ($p<0.05$); However no significant dose response was observed. Analgesia persisted for more than 6 hours with the 2.5 and 3 mg doses	Frequent drowsiness (18 patients on levonantradol)	There was pain relief at all doses, but 67% had one or more side effects (30% of the patients had drowsiness).
Jochimsen et al. (1978)[51] United States	Chronic pain due to malignancies	35	Oral benzopyranoperidene: 2 and 4 mg (synthetic analog of THC); oral codeine: 60 and 120 mg	No analgesic effect of benzopyranoperidine	Sedation equivalent with benzopyranoperidine and codeine	Bezopyranoperidine (2 or 4 mg) is not as effective as codeine (120 mg or 60 mg) and not more effective than placebo in relieving pain due to cancer. Indeed, pain perception appeared to be augmented by both doses.
Staquet et al. (1978)[62] Belgium, United States	Cancer pain	15	Oral Benzopyranoperidine in 4 mg capsules (synthetic analog of THC); oral secobarbital (50 mg capsules)	Superior pain relief with benzopyranoperidine compared to secobarbital and placebo; secobarbital did not exhibit analgesic properties	Drowsiness in 40% of the patients treated with benzopyranoperidine and in 33% of the patients treated with secobarbital	Benzopyranoperidine was superior to placebo and approximately equivalent to 50 mg of codeine phosphate and superior to 50 mg secobarbital. It is not useful clinically because of the frequency of side effects.

Table 4 Multiple Sclerosis

Table 4.1 Randomized Controlled Trials: Smoked Marijuana Cigarettes

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Greenberg et al. (1994)[69] United States	Multiple Sclerosis	20-Placebo Controlled Parallel Group Design	One marijuana cigarette smoked over 10 minutes (1.54% THC); 10 patients Placebo; 10 patients	It was hypothesized that marijuana would remove the spasticity of multiple sclerosis patients sufficiently to allow better postural control. This was measured using a posture measurement system consisting of a stimulus delivery component, a response measurement component and a microcomputer. Dynamic posturography revealed statically significant different presmoking baseline measures. Patients often had the subjective feeling that they were clinically improved, yet postural responses of both normal subjects and patients were adversely affected in terms of noise variance. This observation provides evidence that single exposures to marijuana smoke interfere sufficiently with sensory-motor signal processing to cause even the normal subjects with visual stabilization to revert to a safer postural strategy. Smoking marijuana increased the response delay in patients with eyes closed but not in the normal subjects. Impairment of posture and balance in the 10 patients with multiple sclerosis	Euphoria in all patients smoking marijuana	Smoking one marijuana cigarette containing 1.54% delta 9-tetrahydrocannabinol increased postural tracking error in patients with both eyes open and closed. The tracking error was also accompanied by a decrease in response speed for the patients with their eyes closed. Marijuana smoking further impairs posture and balance in patients with spastic MS.

Table 4.2 Randomized Controlled Trials: Oral THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Freeman et al. (2006)[68] Great Britain	Urge incontinence in Multiple Sclerosis patients	630-This was part of the CAMS study (Zajicek)	Oral THC in capsules; 206 patients. Oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannbinoids per capsule; 211 patients. Maximum dose: 25 mg of THC/ day for 14 days. Placebo-213 patients	From the CAMS study, patients kept incontinence diaries recording urinary incontinence episodes. All three groups showed a significant reduction, $p<0.01$, in adjusted incontinence episode rate (i.e. correcting for baseline imbalance) from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%. Both active treatments showed significant effects over placebo (cannabis extract, $p=0.005$, THC, $p=0.039$)	Generally mild and well tolerated	The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS. This is in contrast to the negative finding of the CAMS study, where no difference was seen in the primary outcome of spasticity.
Svendsen et al. (2004)[71] Denmark	Multiple Sclerosis	24-Plcebo Controlled Crossover Design	Oral THC: 2.5-10 mg per day for 18-21 days	Statistically significant decrease in central pain with oral THC compared to placebo. Median spontaneous pain intensity was significantly lower with THC compared with placebo, 4.0 vs. 5.0 ($p=0.02$) and median pain relief was higher with THC compared with placebo, 3.0 vs. 0.0 ($p=0.035$)	Central and musculoskeletal side effects which required a reduction of the THC dose in four patients. Adverse events, including dizziness, were greater in the treatment group	THC has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, were more frequent than with placebo during the first week of treatment.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Fox et al. (2004)[67] Great Britain	Multiple Sclerosis	14-Placebo Controlled Crossover Design	Oral extracts of *Cannabis sativa* containing 2.5 mg THC per capsule; dose: 5-10 mg of THC BID for 14 days	No beneficial effects on tremors. The primary outcome measured was a change in the tremor index, using a validated tremor rating scale. Secondary outcomes included accelerometry, an ataxia scale, spiral drawing, finger tapping, and nine-hole pegboard test. Analysis showed no significant improvement in any of the outcomes measured. Finger tapping was faster in placebo compared to THC ($p<0.02$).	Generally mild and well tolerated	Cannabis extract does not produce a functionally significant improvement in MS-associated tremor
Zajicek et al. (2003)[77] Great Britain	Multiple Sclerosis	630-Placebo Controlled Parallel Group Design	Oral THC in capsules; 206 patients. Oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannbinoids per capsule; 211 patients. Maximum dose: 25 mg of THC/ day for 14 days. Placebo-213 patients	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale ($p=0.40$). The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0.32 (95% CI -1.04 to 1.67), and for those taking Delta9-THC versus placebo it was 0.94 (-0.44 to 2.31). Treatment effect was seen on patient reported spasticity and pain ($p=0.003$). Improvement in spasticity was reported in 61% of those on cannabis extract, 60% on THC, and 46% on placebo. Subjective improvement in muscle spasms, pain, sleep quality and general condition with both types of cannabinoids. Decrease in hospitalizations for relapses with both types of cannabinoids	Generally mild and well tolerated	Treatment with cannabinoids did not have a beneficial effect on spasticity. However, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.
Wade et al. (2003)[69] Great Britain	Multiple Sclerosis	18-Placebo Controlled Crossover Design	*Cannabis sativa* extract containing THC (2.5 mg), CBD (2.5 mg), or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray in doses of 2.5 – 120 mg/day for four periods of 2 weeks	Statistically significant ($p<0.05$) reduction in spasticity (57.3 vs. 42.3), spasms (58.4 vs. 47.3) and pain (54.6 vs. 44.5) with THC compared to placebo. Statistically significant ($p<0.05$) reduction in pain with CBD compared to placebo (54.8 vs. 44.5). Statistically significant t($p<0.05$) reduction in muscle spasms (55.8 vs. 47.3) and statistically significant improvement in sleep (65.3 vs. 59)quality with the THC-CBD combination compared to placebo. All data is from the daily visual analog scales	Four patients dropped out of the study due to non-tolerated side effects. One could not get benefit without intoxication, one developed a sublingual burning sensation, one had sensitivity to the psychoactive effects if THC, and one had a vasovagal episode.	Cannabis extracts can improve neurogenic symptoms not responsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are neded to confirm these findings.
Killestein et al. (2002)[70] Netherlands	Multiple Sclerosis	16-Placebo Controlled Crossover Design	Oral THC: 2.5 mg capsules BID or 5 mg BID for 4 weeks. Oral *Cannabis sativa* extract in capsules providing 2.5 mg BID or 5 mg BID of THC with 20 – 30% CBD and <5% other cannabinoids for 4 weeks	No benefits on spasticity. Treatment with THC or plant extract worsened the patients' global impression on visual analog scale (THC: $p=0.01$; plant extract: $p=0.02$). Muscle tone was measured using the Ashworth scale. There was no significant change in muscle tone between active treatment and placebo. Worsening was found in the brainstem functional systems score ($F = 4.3$, $p=0.08$) during plant extract treatment	More frequent with the cannabis extract but tolerated. One serious acute psychosis lasting for more than 5 hours did occur with treatment	Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC and plant-extract treatment worsened the participant's global impression.
Ungerleider et al. (1987)[37] United States	Multiple Sclerosis	13-Placebo Controlled Crossover Design	Oral THC: 2.5 -15 mg/day for 5 days	Subjective improvement in patient reported spasticity ratings from the 7.5 mg dose; 2.5 and 5 mg doses ineffective	Frequent from the 7.5 mg dose	At doses greater than 7.5 mg there was significant improvement in patient ratings of spasticity compared to placebo.
Clifford et al. (1983)[65] United States	Multiple Sclerosis	8-Single Blind	Oral THC: 5mg/6 hours. Maximum three doses	Objective improvement in tremors and motor coordination in two patients. One patient experienced a decrease in head and neck tremor with the initial 5 mg dose within 30 to 60 minutes and lasted for about 6 hours. The second patient saw sufficient control in her hand tremor after the 15 mg dose, so much so she could make a legible copy of her name. This was not seen with the 5 or 10 mg doses. Subjective improvement in tremors and well-being in five patients.	Euphoria in all patients with the highest dose uses; dysphoria in two patients	Only 2 of 8 patients responded in this small trial.

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Petro and Ellenberger (1981)[72] United States	Multiple Sclerosis	9-Placebo Controlled Crossover Design	Oral THC, 5 or 10 mg single dose	Significant decrease in spasticity in four patients with both doses of THC ($p<0.01$). Summed scores for the two treatment groups varied significantly from the summed scores for placebo ($p<0.005$). The examiner rated deep tendon reflexes, muscular resistance to stretch in the legs, and abnormal reflexes each on a scale of 0 (absent) to 4 (abnormally increased) and tabulated the total divided by the number of observations as the spasticity score.	Minimal. One patient reported feeling "high" after active treatment. One patient reported feeling "high" after placebo	There was a reduction in spasticity in patients compared to placebo.

Table 4.3 Randomized Controlled Trials: Oral cannabidiol (CBD)

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Wade et al. (2003)[89] Great Britain	Multiple Sclerosis	18-Placebo Controlled Crossover Design	*Cannabis sativa* extract containing THC (2.5 mg), CBD (2.5 mg), or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray in doses of 2.5 – 120 mg/day for four periods of 2 weeks	Statistically significant (p,0.05) reduction in spasticity (57.3 vs. 42.3), spasms (58.4 vs. 47.3) and pain (54.6 vs. 44.5) with THC compared to placebo. Statistically significant ($p<0.05$) reduction in pain with CBD compared to placebo (54.8 vs. 44.5). Statistically significant ($p<0.05$) reduction in muscle spasms (55.8 vs. 47.3) and statistically significant improvement in sleep (65.3 vs. 59)quality with the THC-CBD combination compared to placebo. All data is from the daily visual analog scales	Four patients dropped out of the study due to non-tolerated side effects. One could not get benefit without intoxication, one developed a sublingual burning sensation, one had sensitivity to the psychoactive effects if THC, and one had a vasovagal episode.	CBD can improve neurogenic symptoms not responsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are needed to confirm these findings.

Table 4.4 Randomized Controlled Trials: THC + CBD sublingual spray or oral doses

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Collin et al. (2007)[66] United Kingdom, Romania	Spasticity caused by Multiple Sclerosis	189	THC (2.7 mg) + CBD (2.5 mg)/spray. Max 48 sprays/day: 124 patients. Placebo: 65 patients	Primary outcome measured was change from baseline in the severity of spasticity based on a daily diary assessment of the patient using the Numerical Rating Scale (NRS). For the primary efficacy measure, the adjusted mean change in 11-point NRS spasticity scores for the CBM + THC group at the end of treatment showed a reduction of 1.18 points from a mean baseline period score of 5.49 points. For the corresponding period, the placebo group showed an adjusted mean decrease of 0.63 points from a mean baseline period score of 5.39 points. The estimated treatment difference of 0.52 points, in favor of the CBM group was statistically significant ($p=0.048$; 95% CI: -1.029, -0.004 points)	Dizziness, impaired balance, disturbance in attention, and blurred vision were more common in the CBM +THC group. Dry mouth, urinary tract infections and fatigue were also common. The majority AEs were of mild or moderate severity. There were seven serious AEs, four in the CBM group (3.2%) and three in the placebo group (4.6%). Only one was considered to be possibly related to treatment, a case of vomiting in a subject receiving CBM.	The active preparation is significantly superior to placebo and the treatment was reasonably well tolerated.
Freeman et al. (2006)[68] United Kingdom	Urge incontinence in Multiple Sclerosis patients	630-This was part of the CAMS study (Zajicek)	Oral THC in capsules; 206 patients. Oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannbinoids per	From the CAMS study, patients kept incontinence diaries recording urinary incontinence episodes. All three groups showed a significant reduction, $p<0.01$, in adjusted incontinence episode rate (i.e. correcting for baseline imbalance) from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%. Both active treatments showed significant effects over placebo (cannabis extract, $p=0.005$; THC, $p=0.039$)	Generally mild and well tolerated	The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS. This is in contrast to the negative finding of

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Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
			capsule; 211 patients. Maximum dose: 25 mg of THC/ day for 14 days. Placebo-213 patients			the CAMS study, where no difference was seen in the primary outcome of spasticity.
Wade et al. (2004)[76] Great Britain	Multiple Sclerosis	160-Placebo Controlled Parallel Group Design	Cannabis extract containing almost equal quantities of THC (2.7 mg), and CBD (2.5 mg) administered in sublingual spray at 2.5 - 120 mg/day doses of each constituent for 6 weeks; 80 patients. Placebo; 80 patients	Statistically significant reduction in spasticity with the cannabis extract compared to placebo, evaluated by the VAS scores (objective evaluation) (p=0.001); statistically significant subjective improvement in sleep quality with the cannabis extract compared to placebo; statistically insignificant objective improvement in mobility and vesical dysfunction with the cannabis extract compared to placebo, 10 m walking time improved more with THC + CBD	Generally mild and well tolerated	Spasticity VAS scores were significantly reduced by THC + CBD in comparison with placebo. There were no significant adverse effects on cognition or mood and intoxication was generally mild.
Vaney et al. (2004)[74] Switzerland	Multiple Sclerosis	50-Placebo Controlled Crossover Design	Oral extracts of *Cannabis sativa* containing 2.5 mg of THC and 0.9 mg of CBD per capsule. Dose: 15-30 mg of THC/day for 14 days	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale. In the 50 patients included into the intention-to-treat analysis set, there were no statistically significant differences associated with active treatment compared to placebo, but trends in favor of active treatment were seen for spasm frequency, mobility and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency (P = 0.013) and mobility after excluding a patient who fell and stopped walking were seen (P = 0.01).	Generally mild and well tolerated but more frequent and more pronounced in the treatment group	There were no statistically significant differences associated with active treatment compared to placebo, but trends in favor of active treatment were seen for spasm frequency, mobility and getting to sleep.
Zajicek et al. (2003)[77] Great Britain	Multiple Sclerosis	630-Placebo Controlled Parallel Group Design	Oral THC in capsules; 206 patients. Oral cannabis extract in capsules containing 2.5 mg of THC, 1.25 mg of cannabidiol and less than 5% other cannibinoids per capsule; 211 patients. Maximum dose: 25 mg of THC/ day for 14 days. Placebo-213 patients	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale (p=0.40). The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0.32 (95% CI -1.04 to 1.67), and for those taking Delta9-THC versus placebo it was 0.94 (-0.44 to 2.31). Treatment effect was seen on patient reported spasticity and pain (p=0.003). Improvement in spasticity was reported in 61% of those on cannabis extract, 60% on THC, and 46% on placebo. Subjective improvement in muscle spasms, pain, sleep quality and general condition with both types of cannabinoids. Decrease in hospitalizations for relapses with both types of cannabinoids	Generally mild and well tolerated	Treatment with cannabinoids did not have a beneficial effect on spasticity. However, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.
Wade et al. (2003)[75] Great Britain	Multiple Sclerosis	18-Placebo Controlled Crossover Design	*Cannabis sativa* extract containing THC (2.5 mg), CBD (2.5 mg), or THC + CBD in equal quantities (2.5 mg + 2.5 mg) administered in sublingual spray in doses of 2.5 – 120 mg/day for four periods of 2 weeks	Statistically significant (p,0.05) reduction in spasticity (57.3 vs. 42.3), spasms (58.4 vs. 47.3) and pain (54.6 vs. 44.5) with THC compared to placebo. Statistically significant (p<0.05) reduction in pain with CBD compared to placebo (54.8 vs. 44.5). Statistically significant t(p<0.05) reduction in muscle spasms (55.8 vs. 47.3) and statistically significant improvement in sleep (65.3 vs. 59)quality with the THC-CBD combination compared to placebo. All data is from the daily visual analog scales	Four patients dropped out of the study due to non-tolerated side effects. One could not get benefit without intoxication, one developed a sublingual burning sensation, one had sensitivity to the psychoactive effects if THC, and one had a vasovagal episode.	The & CBD can improve neurogenic symptoms not responsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are needed to confirm these findings.
Killestein et al. (2002)[70] Netherlands	Multiple Sclerosis	16-Placebo Controlled Crossover Design	Oral THC: 2.5 mg capsules BID or 5 mg BID for 4 weeks. Oral *Cannabis sativa* extract in capsules providing 2.5	No benefits on spasticity. Treatment with THC or plant extract worsened the patients' global impression on visual analog scale (THC: p=0.01; plant extract: p=0.02). Muscle tone was measured using the Ashworth scale. There was no significant change in muscle tone between active treatment and placebo. Worsening	More frequent with the cannabis extract but tolerated. One serious acute psychosis lasting for more than 5 hours did occur with treatment	Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
			mg BID or 5 mg BID of THC with 20 – 30% CBD and <5% other cannabinoids for 4 weeks	was found in the brainstem functional systems score (F = 4.3 , p=0.08) during plant extract treatment		and plant-extract treatment worsened the participant's global impression.

Table 4.5 Randomized Controlled Trials: Synthetic Nabilone

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Martyn et al. (1995)[71] Great Britain	Multiple Sclerosis	1-Placebo Controlled Crossover n of 1 Design	Oral nabilone 1 mg/2 days for two periods of 4 weeks	Significant improvement in muscle spasms, pain, general health status and frequency of nocturia. The patient evaluated the effectiveness of treatment at the end of each week by noting the frequency of nocturia the previous night and by use of the visual analog scale to quantify pain and discomfort from muscle spasms.	Minor sedation	Good response from a single patient.

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Table 5 Epilepsy

Table 5.1 Randomized Controlled Trials: Synthetic Cannabidiol

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Cunha et al. (1980)[78] Brazil	Generalized epilepsy inadequately controlled by standard drugs (ages 14-49)	15	Oral cannabidiol 200-300 mg/day for 8-18 weeks; n=8; placebo: seven patients	Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement	Drowsiness reported by four patients on cannabidiol	Some patients that were not controlled on existing regimens exhibited improvement in seizure control. Further studies are needed.

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Table 6 Glaucoma

Table 6.1 Randomized Controlled Trials: Smoked Marijuana Cigarettes

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Merritt et al. (1980)[79] United States	Glaucoma (ages 28-71)	18-Placebo Controlled Crossover Design	One marijuana cigarette containing 2% THC	Marijuana inhalation was accompanied by increased heart rate and decreased intraocular and blood pressure in 18 subjects with heterogeneous glaucoma. The hypotensive effects appeared in 60 – 90 minutes whereas the decrease in IOP appeared to follow the decrease in blood pressure.	Main side effects: various sensory alterations (100%), tachycardia and palpitations (44%), postural hypotension (28%)	Marihuana inhalation was accompanied by increased heart rate and decreased intraocular and blood pressure in subjects with heterogeneous glaucomas. Adverse events occurred with such frequency as to mitigate against routine use.

Table 6.2 Randomized Controlled Trials: THC eye drops

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Merritt et al. (1981)[80] United States	Glaucoma (average age: 65)	8 human subjects with glaucoma and hypertension 8 beagles for parallel design.	Eye drops containing 0.01% (two patients), 0.05% (three patients), or 0.1% (three patients) THC	Reduction in intraocular pressure with 0.05% and 0.1% topical solutions of THC was seen with laboratory animals, though, was not shown effective when administered to six subjects with primary open-angle glaucoma. In laboratory animals administered 0.1% THC, ocular tensions were decreased 3.7 mmHg in the treated eye and 3.4 mmHg in the untreated eye. In human subjects, there was no difference between the 0.05%, 0.1%, and the light mineral oil vehicle (placebo) on either ocular tension, sitting or standing blood pressure, and heart rate. Although, data analysis indicates a definite placebo effect, as light mineral oil alone lowered the ocular tension in the treated eye 5.4 mmHg and 5.0 mmHg in the fellow untreated eye. There was no effect with the 0.01% topical solution of THC	Mild hypotension with the 0.1% topical solution of THC; no psychotropic effects with the 3 THC concentrations administered topically	THC lowers ocular tension in various glaucomas, but at the expense of significant decreases in systolic blood pressure.

Table 6.3 Randomized Controlled Trials: Sublingual THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Tomida et al. (2006)[81] United Kingdom	Glaucoma	6-Placebo Controlled 4 way Crossover Design	One single sublingual dose at 8AM of 5 mg THC, 20 mg CBD, 40 mg CBD, or placebo	Two hours after sublingual administration of 5mg THC, the IOP was significantly lower than after placebo (23.5mm Hg vs. 27.3mm Hg, P=0.026). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9mm Hg (P=0.028).	Vital signs and visual acuity were not significantly changed. One patient experienced a transient and mild panic like reaction after D-9-THC administration. Other side effects reported in at least one patient were oral pain or discomfort, hypotension, and nausea	A single 5 mg sublingual dose of Delta-9-THC reduced the IOP temporarily and was well tolerated by most patients.

Table 6.4 Randomized Controlled Trials: Sublingual Cannabidiol (CBD)

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Tomida et al. (2006)[81] United Kingdom	Glaucoma	6-Placebo Controlled 4 way Crossover Design	One single sublingual dose at 8AM of 5 mg THC, 20 mg CBD, 40 mg CBD, or placebo	Two hours after sublingual administration of 5mg THC, the IOP was significantly lower than after placebo (23.5mm Hg vs. 27.3mm Hg, P=0.026). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9mm Hg (P=0.028).	Vital signs and visual acuity were not significantly changed. One patient experienced a transient and mild panic like reaction after D-9-THC administration. Other side effects reported in at least one patient were oral pain or discomfort, hypotension, and nausea	Administration of 20 mg CBD sublingual did not reduce IOP, whereas 40 mg CBD produced a transient increase in IOP.

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Table 7 Parkinson Disease

Table 7.1 Randomized Controlled Trials: oral THC + CBD

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Carroll et al. (2004)[82] United Kingdom	Parkinson disease	19-Placebo Controlled Crossover Design	*Cannabis sativa* extract containing 2.5 mg THC and 1.25 mg CBD per capsule in a 4-week dose escalation study, maximum dose: 0.25 mg/kg of THC per day	The cannabis extract had no pro- or antiparkinsonian effect. The primary outcome measured was change in the UPDRS (Unified Parkinson's Disease Rating Scale) items 32-34. The overall effect of treatment on dyskinesia score was +0.52, ie worsening, although this failed to reach significance (p=0.09) The cannabis extract had no effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures (Rush scale, Bain scale, tablet arm drawing test, and total UPDRS score following levodopa challenge)	No serious adverse events reports; main side effects: drowsiness/lethargy (9), dry mouth (4), detachment (4). All adverse effects were improved by dose reduction	Orally administered cannabis extract resulted in no objective or subjective improvement in dyskinesias or parkinsonism.

Table 7.2 Randomized Controlled Trials: Synthetic Nabilone

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Sieradzan et al. (2001)[83] United Kingdom	Parkinson disease	7-Placebo Controlled Crossover Design	Oral nabilone: 0.03 mg/kg in two split doses 12 and 1 hours before levodopa administration.	Nabilone had no antiparkinsonian effect per se. Nabilone had no effect on the antiparkinsonian action of levodopa. The best on scores were not significantly different, with a median score of 11 (4-16) with levodopa and nabilone compared with 10 (5-16) with levodopa and placebo. The latency to switching on also was unchanged, with a mean time of 20.7 minutes after levodopa and nabilone treatment compared with 18.3 minutes with levodopa and placebo ($p > 0.05$). There was a significant reduction in total levodopa-induced dyskinesia with nabilone compared to placebo. Thus, the total median total dyskinesia score after treatment with levodopa and nabilone was 17 (11-25) whereas after levodopa and placebo, the median total dyskinesia score was 22 (16-26) ($p<0.05$)	Two patients withdrew from the study, one because of vertigo, the other one due to postural hypotension; five patients experienced transient side effects of mild sedation, "floating sensation", dizziness, hyperacusis, partial disorientation and formed visual hallucinations	The authors demonstrate in this small trial that the cannabinoid receptor agonist nabilone significantly reduces levodopa-induced dyskinesia in Parkinson disease.

Table 8 Tourette's Syndrome in Humans

Table 8.1 Randomized Controlled Trials: Oral THC

Author - Country	Condition Investigated	Sample Size	Intervention	Efficacy	Adverse Effects	Comments
Muller-Vahl et al. (2003)[90] Germany	Tourette's Syndrome	24 (7 dropped out or were excluded)	Oral THC up to 10 mg/day for 6 weeks; 7 patients. Placebo; 10 patients	Decrease in tics with THC compared to placebo. A significant difference ($p<0.05$) or a trend towards significance ($p<0.10$) between THC and placebo on tic ratings at visit 2, 3 and 4 (visit 1, baseline; visit 2-4, during treatment period; visits 5-6, after withdrawal of medication). Tics were rated using the Tourette Syndrome Clinical Global Impression scale, the ShapiroTourette-Syndrome Severity Scale, the Yale Global Tic Severity Scale, the self-rated Tourette Syndrome Symptom List, and a video-tape based rating scale. THC reached efficacy after about 3 weeks of treatment; this efficacy persisted or increased after more than 4 weeks up to the end of the study	THC did not impair cognitive functions; no major adverse effects in most patients; seven patients withdrew from the study but only one patient dropped out of the study due to side effects such as anxiety and agitation	Provides evidence that THC is effective and safe in the treatment of tics, when compared to placebo, but has not been compared to other current treatments.
Muller-Vahl et al. (2002)[91] Germany	Tourette's Syndrome	12-Placebo Controlled Crossover Design	Oral THC: 5, 7.5 or 10 mg in a single dose	Tic severity was assessed using patient rated Tourette Syndrome Symptom List (TSSL), and examiner rated Shapiro Tourette's Syndrome Severity Scale, Yale Global Tic Severity Scale, and Tourette's Syndrome Global Scale. Using the TSSL, patients also reported the severity of associated behavioral disorders. Using TSSL, there was a significant improvement of tics ($p=0.015$) and obsessive compulsive behavior ($p=0.041$) with THC treatment compared to placebo. On examiner rated scores, there was a significant improvement with THC with "complex motor tics" ($p=0.015$), and a trend towards significance with "motor tics" ($p=0.065$), "simple motor tics" ($p=0.093$), and "vocal tics" ($p=0.093$).	No serious adverse effects; five patients experienced mild transient adverse reactions on the nervous system	A pilot study that suggests a single-dose treatment with Delta(9)-THC is effective and safe in treating tics and OCB in Tourette's Syndrome. A more long-term study is required to confirm these results.

Reference List

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